REMARKS

Entry of the instant amendment and reconsideration of the above-identified application as amended is respectfully requested.

Claims 1-16, 18-21 and 28-32 are pending in the application. Claims 1-5 are withdrawn from consideration.

Please cancel claims 1-6, 9, 10, 18 and 20-21.

Claims 1-6, 9, 10, 18 and 20-21 have been cancelled without any prejudice of Applicant's rights to file a divisional application(s) directed to the subject matter cancelled by the instant amendment.

Please add new claims 33-42.

Accordingly, upon entry of the instant amendment, claims 7, 8, 11-16, 19 and 28-42 remain in the application.

Amendments to the Claims

Claim 7 and, therefore, all claims depending from claim 7, have been amended to comprise only those high affinity adenosine A_3 receptor antagonists wherein A is pyrazole.

Furthermore, claim 7 has been amended to include the following claim limitations:

1) Chemotherapeutic agents are limited to those that are characterized by developing P-glycoprotein (P-gp) or multi-drug resistance-associated protein (MRP) dependent multi-drug resistance (MDR); and

2) High affinity adenosine A_3 receptor antagonists are limited to those that inhibit the P-gp or MRP mediated drug-efflux.

Support for the above claim limitations may be found throughout the specification, e.g., second full paragraph on page 7, third full paragraph on page 9, first and second paragraphs on page 13, and the section starting on page 31, last paragraph, and ending on page 33.

Claim 12 has been amended to correct claim dependency.

Claims 8 and 19 have been amended to correct claim dependency, and to comprise only those compounds wherein R^2 is alkyl.

Claims 28-32 have been amended to correct claim dependency.

New claims 33-42 have been added to more adequately cover certain aspects of the present invention.

Claim Rejection under 35 U.S.C. § 112, First Paragraph

Claims 9 and 20 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement, i.e., allegedly there is no teaching in the instant application or in the prior art for the making of the claimed compounds wherein A is a triazolo ring.

Without conceding the correctness of the rejection, claims 9 and 20 have been cancelled, and claim 7 has been amended to only include those compounds wherein A is a pyrazole ring.

In view of the above, it is respectfully submitted that the rejection under 35 U.S.C. § 112, first paragraph, is now moot and should be withdrawn.

II. Claim Rejection under 35 U.S.C. § 103(a)

Claims 6-8, 10-16, 18-19, 21 and 28-32 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6,210,917 to Carson et al. in view of U.S. Patent No. 6,066,642 to Jacobson et al. and further in view of Baraldi et al. "Pyrozolo[4,3-e]-1,2,4-triazolo[1,5-c]-pyrimidine derivatives as highly potent and selective human A_3 adenosine receptor antagonists", Journal of Medicinal Chemistry *42*, 4473-4478 (1999), and Goodman and Gilman, The Pharmacological Basis of Therapeutics.

1) *Carson et al.* teaches a combination therapy comprising an adenosine-5'-triphosphate (ATP) depleting agent to treat cancers such as breast and colon cancer that are multi-drug resistant with respect to vinca alkaloids, taxanes and antibiotics. Carson et al. additionally explains that the depletion of adenosine-5'-monophosphate (AMP) and ATP negatively effects P-glycoprotein activity thereby suppressing MDR.

2) *Jacobson et al.* teaches the use of adenosine A_3 receptor antagonists in the killing of cancer cells (Example 31, column 63) wherein the A_3 receptor antagonists may be used alone or in combination with other pharmaceutically active compounds.

3) *Baraldi et al.* teaches that MRE3008F20 is an adenosine A_3 receptor antagonist.

4) Goodman and Gilman teaches that local means of therapy, such as surgery and irradiation, is routinely followed by adjuvant chemotherapy (page 1225). Goodman and Gilman further teaches that drugs are generally more effective in combination and may be synergistic through biochemical interactions (page 1230).

Clearly, none of the references cited herein above, alone or in combination thereof, suggests that adenosine A_3 receptor antagonists could be employed to inhibit P-gp or MRP mediated drug-efflux in tumor cells thereby suppressing MDR and synergistically enhancing the chemotherapeutic treatment of cancer, as is now discovered and demonstrated by the present invention.

As submitted by Applicants in the communication dated October 3, 2006:

a) The results shown in Tables 4 to 8, starting on page 23, indicate synergistic and unexpected enhancement of the growth inhibitory activity (anti-proliferative activity) of a number of chemotherapeutic cancer agents in the presence of an adenosine A_3 receptor antagonist as determined from the measurement of the enhancement factor (for enhancement and enhancement factor please see a paragraph starting on line 25 on page 12, and a section starting on line 20 on page 16). As the results show, synergistic enhancement of the growth inhibitory activity of taxane compounds, e.g., paclitaxel and docetaxel; vinca alkaloids, e.g., vinblastine; camptothecin compounds, e.g., irinotecan; and antibiotics, e.g., doxorubicin; is observed consistently in the presence of an adenosine A_3 receptor antagonist, e.g., MRE3008F20, IL-10 and IL-11, when tested in different cancer cell lines.

b) The synergistic and unexpected effects of the combination of the present invention are further established, e.g., by colony formation experiments: the adenosine A_3 receptor antagonist MRE3008F20 (10 μM) and the taxane compound paclitaxel (0.75 ng/ml) each alone decreases colony formation of A375 cells to 59 and 64% of the control,

respectively. Surprisingly, when MRE3008F20 is combined with paclitaxel, virtually all colony formation ceases (please see second, third and fourth paragraphs on page 27).

c) Applicants have discovered and demonstrated that adenosine A_3 receptor antagonists, in particular those disclosed in the instant application, are direct inhibitors of P-gp mediated drug-efflux in several cancer cell lines thereby suppressing MDR as summarized in the section starting on page 31, last paragraph, and ending on page 33. For example, MRE3008F20 blocks the P-gp mediated rhodamine 123 (Rh 123) transport in A375 cells completely at 10 μM concentration.

As to the scope of the present invention, it is respectfully submitted that there is no reason to doubt that the corresponding effects can be achieved with any high affinity adenosine A_3 receptor antagonist, i.e., Ki < 50 nM (please see last paragraph on page 9) of the generic formula of claim 7 when combined with any chemotherapeutic cancer agent that is characterized by developing P-gp or MRP dependent MDR.

Additional examples of high affinity adenosine A_3 receptor antagonists within the scope of the generic formula of claim 7 may be found in Baraldi et al., "Pyrozolo[4,3-e]-1,2,4-triazolo[1,5-c]-pyrimidine Derivatives as Highly Potent and Selective Human A_3 Adenosine Receptor Antagonists", *Journal of Medicinal Chemistry* 1999, *42*, 4473-4478 (already on record); Baraldi et al., "Pyrozolo[4,3-e]1,2,4-triazolo[1,5-c]pyrimidine Derivatives as Highly Potent and Selective Human A_3 Adenosine Receptor Antagonists: Influence of the Chain at the N^8 Pyrazole Nitrogen", *Journal of Medicinal Chemistry* 2000, *43*, 4768-4780 (enclosed); Baraldi et al., "Synthesis, Biological Activity, and Molecular Modeling Investigation of New Pyrozolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine Derivatives as Human A_3 Adenosine Receptor Antagonists", *Journal of Medicinal Chemistry* 2002, *45*, 770-780 (enclosed); and U.S. Patent No. 6,921,825 to Baraldi et al.

Claims 6, 10, 18 and 21 have been cancelled, and claim 7 has been amended as described herein above.

In view of the foregoing, reconsideration of the rejection of claims 7, 8, 11-16, 19 and 28-32 under 35 U.S.C. § 103(a) is respectfully requested.

Conclusion

It is respectfully submitted that the subject matter of the instant claims is fully supported by the enabling disclosure of the instant application, and no new subject matter has been incorporated by the above amendments.

In view of the foregoing, the instant application is believed to be in condition for allowance and such is earnestly solicited.

Respectfully submitted,

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Encl.: Supplemental Information Disclosure Statement

Date: November 15, 2007